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DEPARTMENT OF THE ARMY
Fort Detrick
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On the incubation time of experimentally infected animals.

by F. J. Geks.

Zentralblatt f. Bakteriologie, 1. Abt. Orig. 158: 323-325 (1952).

If a group of animals is infected with a positively lethal quantity of bacteria, the animals customarily die after time intervals of different length.

I had the opportunity to investigate this problem, since I was obliged to statistically evaluate the survival time of a large number of mice infected with tuberculosis. In this connection I came upon a noteworthy observation which I have made the subject of my presentation.

Before I make my report, I must remind you of two items:

1. Normal distribution. By this is meant a certain type of frequency distribution which is very often found in biological metric series and which reveals the form of the Gauss error distribution curve; this merely means that the normally distributed magnitude shows the bell-shaped frequency distribution wellknown to all of you.

2. If this bell-shaped frequency distribution is represented as a total curve by adding together the individual percentual frequencies, the well-known S-shaped course is obtained. Finally, this S curve becomes a straight line in the socalled probability grid, a coordinate system in which the ordinate is calibrated according to the Gauss integral. A line in the probability grid therefore is equal to both S and bell curves and indicates, as do the latter two, that a normal distribution is present. Due to the rectilinear course on the probability grid, this representation has the advantage that both the presence of a normal distribution and deviations are readily recognized. In my illustrations, all results are drawn on the probability grid.

The first graph (Fig. 1) represents the evaluation of a test with 63 mice, all of which had received 1 mg TB bacteria intravenously. If the survival time in days is entered on the abscissa and the percentages of animals that died up to the days in question are added thereto, a series of points is obtained which is distinctly convex in its upward course; i.e. the survival time is not normally distributed. If the logarithms of the days are entered on the abscissa in place of days, the curvature is less pronounced; it disappears only when a time constant of 11 days is subtracted from the survival time of each individual mouse and the survival time diminished in this manner is entered in logarithm on the abscissa. A repetition of this experiment with 68 animals yielded the same result (Fig. 2). Here, too, the rectilinear bearing is obtained only after the subtraction of the time constant of 11 days. These findings are in opposition to those of American authors (1,2) who claim to have observed a normal distribution of the survival time already in

connection with the numerical calibration of the abscissa.

Owing to this difference and in order to obtain greater certainty on the reality of this time constant, I have conducted an identical test with mice infected with streptococci (Fig. 3). The result was basically the same. If the survival time -- now in hours, since the animals succumb to this infection more rapidly -- is entered on the abscissa and the percentages of the total animals dead at the end of each hour is added thereto, a bent curve is obtained which is less curved upon conversion to logarithmic hours, but becomes linear only upon the subtraction of a time constant, in this case 16.5 hours.

In 1943 Cavalli and Magni (3) have treated this problem without finding a satisfactory solution. I have analysed the only one of their extensive tests in which all animals died, in the same manner. The test deals with 191 mice infected with pneumococci. Here, too, the same picture was obtained (Fig. 4). If the hours or their logarithms are entered on the abscissa, a series of points is obtained which curve upward in a convex course, becoming linear when a time constant (9 hours in this case) is subtracted.

I have found an affirmation of my observations in an area farther removed from mine. The Swede Liljestrand (4) in investigations of salvarsan in 1949, has graphically depicted the survival time of mice infected with *Tryp. equiperd*. (Fig. 5). In this connection he has failed to find a normal distribution in both numerical and logarithmic scales of the abscissa. It was obtained only when a constant was subtracted from the survival time of each animal, in this case 52 hours.

The findings enumerated here ought to have shown that a time constant characteristic of the type of infection and its dose has a part in the course of a lethal experimental infection, the reality of which in my opinion is no longer in doubt. It seems particularly remarkable to me that this magnitude is independent or at least extensively independent of the individuality of the animal. It should be the goal of additional research to gain information on the significance or the biological meaning of this time constant. Initial attempts at elucidation do not rise above the stage of hypothesis. I have therefore limited myself to the reporting of facts. In closing, it is perhaps appropriate to mention an idea that seems worthy of expression because it admits of rather interesting conclusions, namely that the time constant might be identical with the incubation time.

GRAPHS

- Fig. 1. Survival time of 63 mice after 1 mg TB bacteria i.v.
- Fig. 2. Survival time of 68 mice after 1 mg TB bacteria i.v.
- Fig. 3. Survival time of 42 mice after 0.2 ml $4 \cdot 10^{-4}$ Str. Aronson.
- Fig. 4. Survival time of 191 mice infected i.p. with pneumococci (after Cavalli et al.)
- Fig. 5. Survival time of 40 mice infected i.p. with *Tryp. equiperd*. (after Liljestrand)

LITERATURE

1. McKee, C.M., Rake, G., Donovick, R., and Jambor, W.P., Amer. Rev. Tbc. 60, 90-108 (1949). — 2. Donovick, R., McKee, C.M., Jambor, W.P., and Rake, G., Amer. Rev. Tbc. 60, 109-120 (1949). — 3. Cavallii, L., and Magni, G., Zbl. Bakter. I Orig. 150, 353-371 (1943). — 4. Liljestrand, A., J. Pharm. a. Pharmacol. 1, 78-86 (1949).

Author's address: Dr. med. Franz J. Geks, Brackwede/Westf., Asta-Werke A.G., chem. Fabrik.